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Anatomical Evaluation of Mandibular Bone Cortex in Patients with Mucopolysaccharidosis: A Case-Control Study

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Aims: To evaluate the mandibular bone cortical of patients with mucopolysaccharidosis on panoramic radiograph, through radiomorfometric indices.
Study Design: Case-control study.
Place and Duration of Study: Sample: Department of Diagnostic Imaging of the *Universidade Estadual da Paraíba*, Campus VIII, in the city of Araruna, PB, between January and December of 2015.
Methodology: Panoramic radiographs of sixteen patients with mucopolysaccharidosis and 32 controls, organized by gender and age, composed the sample. The mandibular panoramic index, gonial index, antegonial index and mental index were evaluated. Pearson's Chi-square test,

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Fisher's exact test and Mann-Whitney test were used to statistical analysis with a level of significance of 5.0%.
Results: Mucopolysaccharidosis patients were mostly female (62.5%), with a mean age of 12.31 + 7.16 years, MPS VI (50.0%) being the most prevalent. Patients with mucopolysaccharidosis had higher values in the gonial (1.86±0.48), the antegonical (4.36±1.24) and the mental (5.24±1.21). However, only the antegoniac index presented a significant difference (*P*=0.047).
Conclusion: The antegoniac index was higher in patients with mucopolysaccharidosis and the other radiomorphometric measures were similar to those observed in the control group. Apparently, mucopolysaccharidosis is not related to decreased bone to mandibular quality.

Keywords: Panoramic radiography; mucopolysaccharidosis I; mucopolysaccharidosis IV; mucopolysaccharidosis VI.

1. INTRODUCTION

Mucopolysaccharidosis (MPS) is a hereditary lysosomal disorder caused by deficiencies in enzymes that catalyze the breakdown of glycosaminoglycans (GAGs). The progressive lysosomal accumulation of GAGs results in serious growth deficit, skeletal deformities (multiple dystoses), poor joint mobility, thick facial features and enlarged organs. Eleven known enzyme deficiencies give rise to seven distinct types of MPS (I-IV, VI, VII and IX). The prevalence of MPS ranges from 1.9 to 4.5/100,000 live births, with the occurrence of geographic differences in the frequencies of specific types of the disease [1-4].

MPS has a chronic, progressive, clinical course and a multi-systemic nature. The main characteristics are short stature, mental retardation, multiple dystoses, cardiovascular and digestive impairments, ocular abnormalities and dermal infiltrations of accumulated products due to metabolism errors. Patients with more serious forms of the disease have low longevity (mean: 10 years), whereas those with milder forms have relatively normal longevity [1-5].

From the dental standpoint, macroglossia is often found associated with anterior open bite, delayed eruption and impaction of permanent teeth, gingival hyperplasia, hypertrophy of the alveolar processes, high arched palate and hyperplasia of dental follicles [6-8]. Individuals with MPS also have a greater prevalence rate of dentigerous cysts, impacted teeth, hypoplasia and structural bone abnormalities [5,6,9,10]. Abnormalities of the maxillomandibular complex are frequent in patients with type VI MPS [8].

As this condition induces bone abnormalities, the measurement of radiomorphometric indices used in the study of bone quality can be identified in a routine panoramic radiograph, which is a practical, low-cost exam. The aim of the present study was to evaluate the mandibular bone cortex using radiomorphometric indices in panoramic radiographs of patients with MPS.

2. METHODOLOGY

This cross-sectional case-control study was developed with patients with MPS, in Brazil. The following were the inclusion criteria for the case group: a cytogenetic diagnosis of MPS; absence of any type of surgical or orthodontic intervention; and panoramic radiographs of good quality (no distortions, maximum detail and medium degrees of density and contrast). Non-probabilistic sampling was performed with a convenience sample. The control group comprised two individuals matched for sex and age for each patient in the case group. The final sample was composed of 16 patients with MPS and 32 controls.

Panoramic radiographs were obtained using the ORTHOPHOS XG 5 (DS Ceph, Sirona, Bensheim, Hessen, Germany) operating at 90 kV and 15 mA, following the manufacturer's instructions. All biosafety norms were followed, with the essential control of biological risk and radiation.

A clinical chart was used containing data on sex, age, type of MPS and the following measurable radiomorphometric indices: antegonial index (AI), gonial index (GI), mental index (MI) and panoramic mandibular index (PMI), as shown in Fig. 1. These indices are based on cortical bone measurements, which are more easily visualized in radiographs than cancellous bone [11].

The AI refers to the thickness of the cortex of the mandible in the anterior region of the mandibular

angles (gonia) and is obtained by tracing a tangent from the anterior edge to the lower edge of the ascending ramus. This line crosses another line tangent to the lower edge of the mandible, obtaining a line perpendicular, on which the index is measured and should be ≥ 3.2 mm [12]. The GI is obtained when two lines are traced – one tangent to the lowermost point of the gonial angle and lower edge of the mandibular body and another tangent to the posterior edge of the ramus and head of the mandible. The intersection of these two lines forms the gonial angle, the measurement of which should be > 1.2 mm [13]. For the MI, the inferior thickness of the mandible is measured on a line below the mental foramen perpendicular to a line tangent to the lower edge of the mandible and its measurement should be ≥ 3.1mm [12,14]. The PMI is obtained from the division of the measure of the thickness of the mandibular cortex in the region of the mental foramen by the distance from the inferior or superior edge of mental foramen to the edge of the mandible, which should be > 0.3 mm [15].

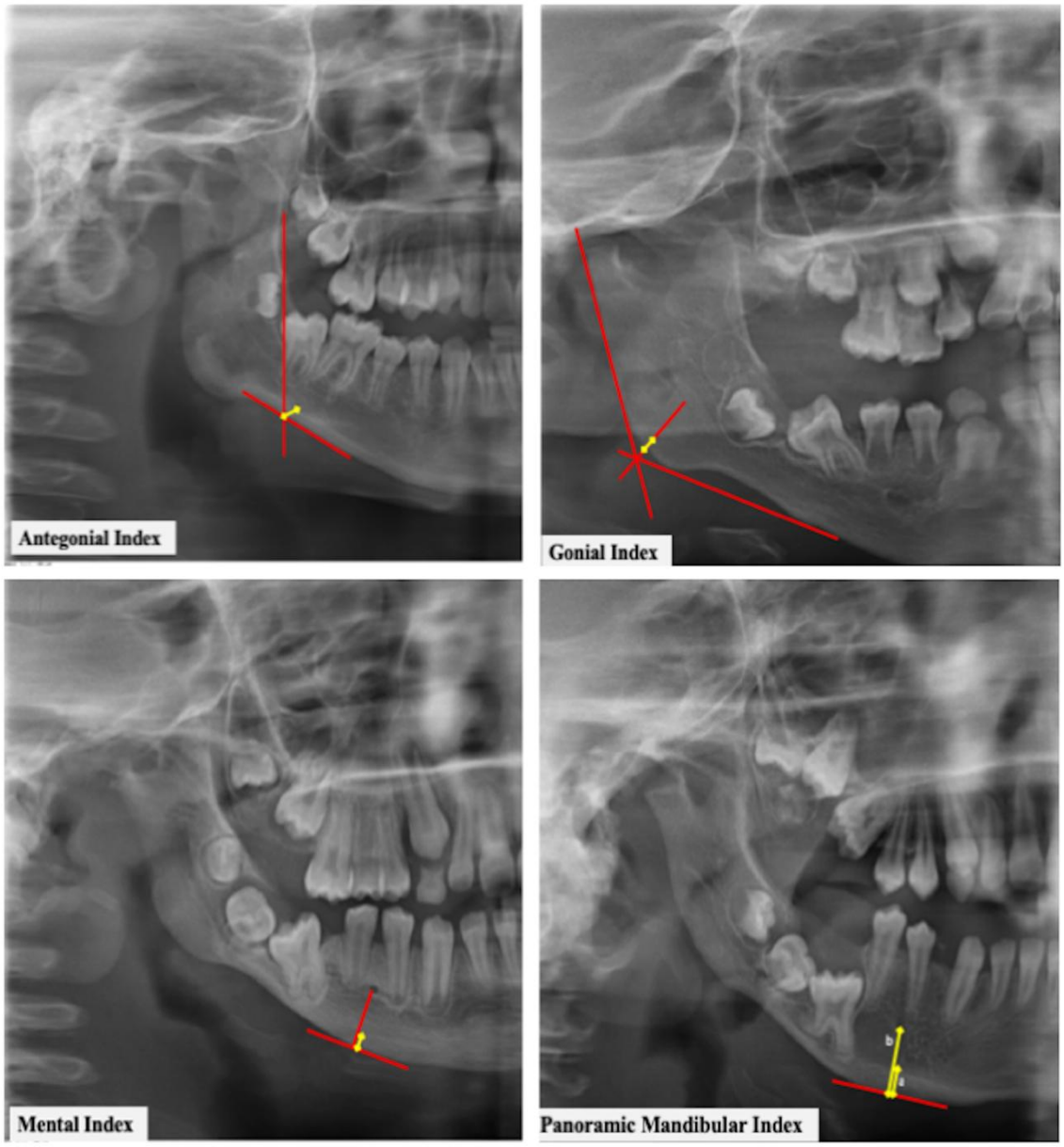

Fig. 1. Antegonial index (AI), gonial index (GI), mental index (MI) and panoramic mandibular index (PMI)

The measurements of those indices were performed bilaterally on the images of the panoramic radiographs with the aid of ImageJ 1.49v (Wayne Rasband National Institute of Health, USA, Java 1.6.0_20 [32-bit]). Each radiomorphometric index was analyzed by a duly calibrated, blinded evaluator. The measurements were performed three times by the same evaluator, with a one-week interval between readings. The mean of the three readings was used in the statistical analysis.

The Statistical Package for the Social Sciences (version 20.0; SPSS Inc., Chicago, IL, USA) was used for the descriptive analysis. Comparisons of the indices between groups were performed with Pearson's chi-squared test, Fisher's exact test and the Mann-Whitney, with the level of significance set to 5% ($P < 0.05$).

3. RESULTS

The sample was composed of 48 individuals: 16 patients with MPS and 32 controls. The majority of the patients with MPS were female (n = 10; 62.5%) and mean age was 12.31 ± 7.16 years. The most prevalent type of MPS was VI (n = 8; 50%), followed by IV (n = 7; 43.7%) and I (n = 1; 6.3%).

In the dichotomized analysis (without alteration/altered) of the MPI, GI, AI and MI, no statistically significant differences were found between the case and control groups, as similar proportions of alterations for each index were found in each group (Table 1).

In the comparison of the median values of the indices, the case group had a higher GI, AI and MI, whereas the control group had a higher MPI. However, only the AI differed significantly between groups (Table 2).

4. DISCUSSION

Despite the important manifestations of MPS in childhood, there continues to be an approximately five-year delay in the diagnosis of these patients in Brazil. Strategies are needed that can facilitate the diagnosis and enable the recognition of these alterations as early as possible [10]. This investigation is the first study to evaluate the mandibular cortex in patients with MPS using radiomorphometric indices, which were created to qualify and quantify mandibular bone and its correlation with bone cortices. These indices can be used to investigate systemic conditions, such as osteoporosis, in which the mandibular cortex is diminished [16].

The most frequent type in Brazil is MPS I, followed by MPS II and MPS VI. In the present study, the most frequent type was MPS VI. Oral abnormalities, such as anterior open bite, was the most exclusive finding in patients with MPS VI [9], whereas generalized enamel hypoplasia was exclusively found in patients with MPS IV [5,9].

Table 1. Comparison of cases and controls according to alteration in radiomorphometric variables

Variable		Group		
		Case n (%)	Control n (%)	*P* (1)
Panoramic mandibular index	**Without alteration**	6 (37.5)	11 (34.4)	0.831 (2)
	Altered	10 (62.5)	21 (65.6)	
Gonial index	**Without alteration**	13 (81.3)	28 (87.5)	0.672 (1)
	Altered	3 (18.7)	4 (12.5)	
Antegonial index	**Without alteration**	13 (81.3)	21 (65.6)	0.328 (2)
	Altered	3 (18.7)	11 (34.4)	
Mental index	**Without alteration**	16 (100.0)	31 (96.9)	1.000 (2)
	Altered	0 (0.0)	1 (3.1)	
TOTAL		16 (100.0)	32 (100.0)	

(1) Pearson's chi-squared test; (2) Fisher's exact test

Table 2. Sample size, mean, standard, median, 25 and 75 quartiles and post mean for the comparison of radiomorphometric indices between cases and controls

Group	n	Mean ± standard deviation	Median	Q_{25}-Q_{75}	Post mean	$P^{(1)}$
Panoramic mandibular index						
Case	16	0.26 ± 0.09	0.21	0.19-0.32	21.03	0.225
Control	32	0.27 ± 0.08	0.25	0.23-0.33	26.23	
Gonial index						
Case	16	1.86 ± 0.48	1.96	1.47-2.10	26.50	0.484
Control	32	1.72 ± 0.53	1.68	1.43-2.09	23.50	
Antegonial index						
Case	16	4.36 ± 1.24	4.92	3.01-5.38	30.19	0.047*
Control	32	3.48 ± 0.95	3.35	3.13-3.94	21.66	
Mental index						
Case	16	5.24 ± 1.21	5.17	4.11-6.22	27.44	0.304
Control	32	4.74 ± 1.35	4.46	3.95-5.74	23.03	

(*) significant difference to 5.0%
(1) Mann-Whitney test

Age and sex exert an influence on radiomorphometric indices. These indices tend to diminish over time until reaching 75 years of age and diminish more rapidly in women than men [16,17]. Bajoria et al. [16] demonstrated that women have smaller means than men, suggesting that the reduction in the gonial and antegonial indices is related to osteoporosis. In the Brazilian population, Alonso et al. [18] also found significant differences related to age and bone quality between sexes, with women exhibiting lower bone density indices than men. As these findings confirm the influence of age and sex on bone quality, such aspects may have affected the results of the present investigation. However, no analysis of these aspects was performed, which constitutes a limitation of the study.

Dental radiographs with proper technique are important indicators for the analysis of osteoporosis [19] and recent studies have used this resource for such a purpose [20-23]. No previous studies have analyzed radiomorphometric indices in patients with MPS. However, the fact that this disease involves serious bone abnormalities at an early age justifies the evaluation of such indices in these patients.

The mental index is used to determine the quantity of mandibular bone in panoramic radiographs and determine signs of resorption [16]. Although no evidence of a significant alteration in this index was found in the patients with MPS in the present study, Kiswanjaya et al. [24] and Hastar et al. [25] assessed bone quality in older individuals and found that the MI diminished with age and was lower in whites than blacks [24,25]. Analyzing digital radiographs, Govindraju and Chandra [26] found significant differences in the MI between men and women with osteoporosis. Ledgerton et al. [14] reported that this index is lower in women, especially those with osteoporosis.

Ledgerton et al. [12] found a mean antegonial index of 4.46 mm. When the authors proposed the index in 1997, they reported that the mean should be equal to or greater than 3.2 mm. In the present study, the mean of this index met the criterion stipulated by the authors. However, despite the lack of a statistically significant difference between groups, the AI was altered in a considerable percentage of the patients with MPS, which may be associated with the inherent skeletal deformities that accompany the disease. Comparing bone patterns between healthy men (controls) and those with osteoporosis (cases), Cakur et al. [27] found that the mean AI was 5.21 mm in the control group and 4.17 mm in the case group. This mean in the case group is lower than that found for the patients with MPS in the present investigation. Dagistan et al. [28] compared the AI between healthy men and those with kidney failure and found means of 4.41 and 3.00 mm, respectively. The mean in the case group was also lower than that found in the present investigation. Those authors [28] also found a statistically significant difference in the AI between groups, which is in agreement with the present findings. Only males participated in the two studies cited to avoid the effects of hormonal changes in menopause. While this was not an

exclusion criterion in the present study, the females with MPS in the sample were not in menopause, which justifies their inclusion.

Acceptable gonial index values should be larger than 1.2 mm [12], which occurred in both groups in the present study. In contrast, Bajoria et al. [16] found means of 1.13 mm and 0.77 mm in men and women, respectively. This difference may be explained by the greater mean age of the patients in the study cited (45.48 years) compared to the younger patients in the present investigation.

Kwon et al. [29] explored the usefulness of the panoramic mandibular index for the evaluation of bone mineral density and stressed the limitation of this index when it is not possible to locate the mental foramen. The literature reports that this index diminishes over the years [16,30], but one study reports that the PMI tends to increase with age [15] Due to the difficulties regarding the measurement of this index, the calibration of the evaluators and the quality of radiographic images, the applicability of the PMI for bone assessments continues to be controversial. Bajoria et al. [16] and Dagistan and Bilge [30] demonstrated that the PMI diminishes over the years and is also lower in women than men. In the present study, both groups (case and control) had a lower mean PMI than the established value, but with no significant difference between groups. This finding may be due to the measurement differences stemming from the program used or the fact that the panoramic radiographs exhibited positioning flaws inherent to the posture of the patients with MPS and individuals in the control group, the majority of whom were children.

Understanding the severity and extent of radiographic maxillomandibular alterations is the first step toward the planning of strategies to promote early intervention and attenuate the gross facial features that occur in patients with MPS. The evaluation of the bone cortex using radiomorphometric indices may constitute a good indicator of the bone status of patients with this disease. However, the scarcity of articles on this topic underscores the need for further studies (preferably with a longitudinal design) for a better exploration of this population and the confirmation of the present findings.

According two reviews [31,32], an early treatment with enzyme replacement therapy (ERT) can improve the patient prognosis. However ERT does not have enough impact on bone and cartilage lesions in patients with MPS. In addition, late introduction of ERT can result in malocclusion, such as protrusion in those patients [33].

5. CONCLUSION

The majority of patients with mucopolysaccharidosis were female, with a mean age of 12.31 ± 7.16 years, and the most frequent type of the disease was MPS VI. The antegoniac index was higher in patients with MPS; the other radiomorphometric measures were similar to those observed in the control group. Apparently, MPS is not related to decreased bone to mandibular quality.

CONSENT

The consent was obtained from patients and the study was performed in accordance with the Declaration of Helsinki.

ETHICAL APPROVAL

The study was approved by the Research Ethics Committee (protocol number: 35761914.5.0000.5187) and was conducted in accordance with Resolution 466/12 of the Brazilian National Health Council.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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